

Hypocholesterolemic Effect of Human Growth Hormone in Coronary-Prone (Type A) Hypercholesterolemic Subjects¹ (36719)

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Several years ago we demonstrated (1, 2) that growth hormone (GH) played a part in the regulation of the serum cholesterol of the rat. In accord with this observation, Merimee and Hollander (3) recently have reported that the average serum cholesterol level of sexual ateliotic dwarfs exhibiting a monotropic deficiency of GH, was markedly elevated (438 mg/100 ml). It thus would appear that in the human subject also, the presence of GH is a requisite for a normocholesterolemic state.

Quite independent of our animal studies, we recently studied the GH responses to an infusion of arginine of 10 human subjects, exhibiting the coronary-prone Type A behavior state (4). We found (5) that the majority of these subjects, when infused with arginine *in their own usual economic or professional milieu, i.e.,* during an ordinary business day, failed to exhibit an increase in plasma growth hormone levels as large as that observed in the control Type B subjects. Since six of these ten Type A subjects also were chronically hypercholesterolemic (*i.e.,* their serum cholesterol exceeded 270 mg/100 ml), their poor GH response to arginine, when considered with the above experimental findings, suggested the possibility that their serum cholesterol levels might be reflectant of a functional deficit of GH. We therefore decided to administer human growth hormone (HGH) to Type A hypercholesterolemic men. The preliminary results reported below indicate that such administration promptly lowered the serum cholesterol level of each of the 4 subjects.

Four apparently well, Type A, moderately hypercholesterolemic male subjects (av age, 48 years; av height, 71 in.; av wt, 196 lb) volunteered for this study to determine some of the acute effects of human growth hormone (HGH) administration upon their serum lipid levels. These subjects previously had volunteered for many of our earlier studies and their serum cholesterol values consistently had been found elevated over the past 4-5 yr. Each subject agreed to continue his usual habits of eating, drinking, exercising and working during the 2 week control period prior to the third week during which HGH was self administered and also during the three weeks after the cessation of HGH administration.

At the beginning of week 1, after an overnight fast of 14 hr, sufficient blood was taken from each man for analyses of the serum cholesterol (6), triglyceride (7), free fatty acid (FFA) (8), glucose (9), lipoprotein (10), cortisol (11), thyroxine (12), and growth hormone (13) levels. Immediately following this bleeding, 100 grams of glucose were given to 3 of the 4 subjects and additional blood samples were obtained 60 and 120 min later. These latter 2 samples were analyzed for their serum glucose levels. The subjects then were instructed to record their dietary intake each day for 7 days in order to determine their average daily intake of protein, carbohydrate, fat (saturated and polysaturated) and cholesterol.

At the beginning of week 2, the fasted subjects again were bled in the morning and blood samples were analyzed again for serum cholesterol, triglyceride (TG), FFA, lipoprotein, glucose and GH levels. Several days later, each of the subjects, after a rest of 30 min, was infused for 30 min with arginine as

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previously described (5). Only one of these subjects (Case 1), however, had been exposed to his usual economic milieu on the day of the test. Blood samples obtained before, and 30, 60 and 90 min after the beginning of the infusion were analyzed for their growth hormone (GH) concentration. During week 2, all subjects also began testing their own urine each morning with Labstix reagent strips (Ames Co.) for the possible presence of excess glucose, protein and ketones. This last procedure was instituted in order to obtain control analyses prior to the daily urine testing that would be done when the subjects administered human growth hormone (HGH) to themselves.

At the beginning of week 3, the fasted subjects were bled and the same analyses done at the beginning of week 2 were repeated. Following the obtaining of this blood sample, each subject (after appropriate instructions had been given) injected himself subcutaneously with 5 mg of purified HGH, prepared as previously described (14), and continued to inject himself with this same amount each AM and PM for 7 days. During this same third week, the subjects also again recorded their daily intake of food. Because of the tendency of HGH to cause the retention of excess sodium, the subjects weighed themselves daily and if any of them gained more than one pound in 24 hr, he ingested 40 mg of furosemide (Lasix).

At the end of week 3 (12 hr after their final injection of HGH) the subjects were bled and then the same 3 of the 4 subjects initially given the glucose tolerance test again were given 100 g of glucose. Additional blood samples then were obtained from these 3 subjects, 60 and 120 min later. The fasting and the two postprandial blood samples were analyzed as at the beginning of week 1.

The subjects finally were bled weekly for 3 weeks after the termination of the HGH administration and the same analyses were obtained on these samples as were obtained on the blood samples withdrawn at the beginning of week 2. In addition, a third glucose tolerance test was done on the same three initially tested subjects, 2 weeks after the end of the HGH administration.

Results. The average Serum GH level of the four subjects was 4.7 ng/ml before arginine infusion and their average peak value after arginine was 7.6 ng/ml, a value below the average of 12.4 ng/ml previously observed (5) in normal Type B subjects.

The dietary intake of the four subjects before administration of HGH (2221 cal/day) was essentially the same as that (2243 cal/day) taken during its administration. The body weight of the four subjects also remained unchanged during the 1 wk of HGH treatment.

The administration of HGH decreased the glucose tolerance of each of the three subjects who were studied in this regard. Thus their average blood glucose concentration before and then 1 and 2 hr after ingestion of glucose was 86, 128 and 85 mg/100 ml, respectively, before HGH treatment and 101, 191 and 193 mg/100 ml during such treatment. This probably HGH-induced abnormality however appeared to be transient because when this test was repeated on these same three subjects 2 wk after the termination of HGH treatment, the glucose tolerance again became normal in each subject.

No significant changes were observed in the serum T_4 or cortisol levels during the HGH administration. The average serum GH level of the four subjects prior to HGH treatment was 4.3 ng/ml and was 9.7 ng/ml, 12 hr after the final dose of HGH.

The serum cholesterol content of each of the four subjects fell (see Table I) following the 7 day administration of HGH only to rise to their preinjection levels during the 3 wk following cessation of the HGH injections. Submission of their cholesterol values to a 2-way analysis of variance and to the Student-Newman-Keul test [cited in (15)] indicated that their average serum cholesterol value (241 mg/100 ml) at the beginning of week 4 (*i.e.*, their serum cholesterol level after 7 days of HGH administration) was significantly different ($p < .01$) both from the three weekly cholesterol values obtained before and the three weekly cholesterol values obtained after the 1 wk treatment of HGH had been given.

Concomitant with the fall in the average

TABLE I. Serum Lipid Values Before, During, and After Administration of HGH Fasting Serum.

Week	Case	Chol. (mg/100 ml)	TG (mg/100 ml)	FFA (mEq/liter)	Lipoproteins (%)		
					Prebeta	Beta	Alpha
1	1	284	162	707	21	54	25
	2	283	161	767	22	54	24
	3	316	147	740	27	40	33
	4	262	309	980	42	34	24
	Av	286	195	799	28	46	26
2	1	316	121	883	20	53	27
	2	318	164	780	22	50	28
	3	312	195	699	25	48	27
	4	284	226	1051	39	34	27
	Av	308	177	853	27	46	27
3 Beginning of week	1	310	85	999	18	57	25
	2	312	127	785	17	55	28
	3	324	137	1028	24	55	21
	4	252	198	759	40	35	26
	Av	300	137	893	25	50	25
3 End of week*	1	238	229	1220	42	34	24
	2	254	272	878	33	38	29
	3	260	218	781	30	40	30
	4	211	223	759	36	34	30
	Av	241	236	910	35	37	28
4	1	276	84	743	6	58	36
	2	339	180	856	17	53	30
	3	303	142	754	19	54	26
	4	246	144	867	31	48	21
	Av	291	138	805	18	53	28
5	1	316	82	743	6	58	36
	2	323	125	1070	22	54	24
	3	317	189	590	27	52	21
	4	236	270	978	40	33	27
	Av	298	167	845	24	49	27
6	1	315	82	916	13	42	45
	2	330	130	811	20	50	30
	3	317	118	673	22	42	36
	4	262	240	1143	36	34	30
	Av	306	143	886	23	42	35

* Serum lipid values 12 hr after 7 days of twice daily injections of 5 mg HGH.

serum cholesterol observed during the administration of HGH, the serum TG and prebeta lipoprotein levels of these four subjects were observed (see Table I) to increase. Submission of the average values of serum TG and prebeta lipoprotein to the same statistical analyses described above, indicated that both these rises observed during the administration of HGH were significant ($p < .01$). As

Table I depicts, the rise in the prebeta lipoprotein fraction was accompanied by a corresponding fall in the beta lipoprotein fraction. No significant difference was observed in the serum FFA level (see Table I) of these three subjects before, during or after the administration of HGH.

Discussion. We initiated this present study primarily to determine whether the ad-

ministration of HGH to human subjects, exhibiting both the coronary-prone Type A behavior pattern and a hypercholesterolemia, might alter the latter state. We had some reason to suspect that such alteration might take place because of two earlier observations. The first one was our finding (1, 2) that the presence of growth hormone was requisite for the normal control of serum cholesterol level in the rat. From the recent observations of human dwarfs lacking GH, made by Merimee and Hollander (3), the presence of GH also is seemingly necessary for the normal control of serum cholesterol in man. Our second observation was the detection (5) of a functional depletion of GH in most subjects exhibiting both the above behavior pattern and a hypercholesterolemia.

The results of this preliminary study indicate that the administration of HGH did reduce the elevated serum cholesterol level of these particular hypercholesterolemic subjects. Indeed, each of the serum cholesterol values observed at the end of 7 days of HGH administration was not only significantly lower than those observed in this particular study, in the several weeks prior to and after the period of HGH administration, but they also were the lowest ever observed in these subjects during the 4-5 yr in which their cholesterol values had been monitored in other studies. Whether, however, the administration of HGH effected this fall in serum cholesterol level because it fulfilled a *specific* need for this hormone in our four subjects or because its administration was capable of lowering the serum cholesterol in all types of hypercholesterolemic subjects (and even normocholesterolemic subjects) requires considerable further study.

The fall in serum cholesterol observed in each of our four subjects after seven days of HGH administration was accompanied by a significant rise in the serum triglyceride level of each subject. The prebeta lipoprotein fraction of the lipoprotein spectrum also rose significantly. The fasting serum FFA levels of these subjects however showed no change. The continuing normality of the fasting blood sugar but impairment of glucose tolerance observed in our subjects while taking HGH

confirms the findings of previous workers (16, 17).

While none of our subjects complained of nausea, two complained of a slight myalgia and an early morning headache which was easily abolished by aspirin. All such symptoms disappeared within 12 hr after discontinuance of HGH injections.

Summary. The administration of human growth hormone to four hypercholesterolemic, coronary prone (*i.e.*, exhibiting Type A behavior pattern) subjects led to a significant fall in their average serum cholesterol level and a significant rise in their average serum triglyceride and prebeta lipoprotein levels. The glucose tolerance was impaired significantly but transiently during HGH treatment.

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